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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/964,065	09/26/2001	Imre Kovesdi	212357	1431

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EXAMINER	
PRIEBE, SCOTT DAVID	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 08/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/964,065	KOVESDI ET AL.	
	Examiner	Art Unit	
	Scott D. Priebe, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 January, 16 March, and 13 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *53-60,63-70,73-88 and 91-98* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *53-60,63-70,73-88 and 91-98* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *20060125*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 1/25/06 has been entered.

The Art Unit designation of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Primary Examiner Scott D. Priebe, Ph.D., Group Art Unit 1633.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

Claims 53-60, 63-70, 73-88, and 91-98 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for systems with a cell and methods using the system wherein the adenovirus E2A or E4 region in the cellular genome is operably linked to an inducible or repressible promoter, does not reasonably provide enablement for embodiments wherein it is linked to a promoter which is not inducible or repressible. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly

connected, to make and use the invention commensurate in scope with these claims. This grounds of rejection is essentially the same as applied to cancelled claims 36-38, 40-43, and 45-47 in the Office action of 2/27/02. This grounds of rejection was inadvertently omitted following the addition of claims 53-72 in the RCE request of 11/22/02.

Claims 53-60, 63-70, 73-88, and 91-98 recite no limitation on the promoter used to express adenoviral E4. The specification (paragraph bridging pages 14-15) describes the importance of using inducible or repressible promoters to express adenoviral sequences in the cell lines, specifically mentioning E2A and E4. All of the exemplified cell lines which are disclosed as being capable of producing adenovirus lacking E2A or E4 have nucleic acid sequences encoding products complementing the E2A and E4 regions which are operably linked to an inducible promoter. The use of an inducible or repressible promoter which directs low levels of expression except when induced (or derepressed) is the only means taught in the specification for obtaining production of viable cells which can complement deficiencies of essential genes of the E2A and E4 regions. The specification also teaches that repressible promoters can be used, rather than inducible promoters, where derepression is used to induce expression of E2A and E4 at the desired time.

Those skilled in the art recognized that expression of the E1, E2A and E4 genes is disruptive of normal cell metabolism, so that the transcription regulatory sequences used to control expression of the E2A and E4 genes in the host cells must be used which reduced expression to low levels during cell growth, and which can be induced to higher activity when the cells are used to produce the recombinant adenovirus (Klessig et al. (1984) Mol. Cell. Biol. 4(7), pp. 1354-55; Wang et al. (1995) Gene Ther. 2, pp. 779-780; and the Declaration of Dr.

Kovesdi filed 5/13/96 in application 08/258,416, pp. 5-7). Armentano et al. (Hum. Gene Ther. 6: 1343-1353, 1995) in discussing the prior and post-filing art (page 1344, col. 1, full para. 1) disclose that despite extensive knowledge for development of adenoviral vectors, little success had been reported on vector genome modifications, being limited to deletions of E1 and E3. With respect to replication defective vectors, the reference discusses propagation of defective virus on complementation lines, and states that "This approach is problematic in principle due to the large number of structural and regulatory genes, many of which are temporally regulated, function stoichiometrically, and may be toxic to cells at levels required for complementation." It also discloses that "the 293 cell line was difficult to produce initially and there are few, if any, reports of similar cell lines stably expressing E1 functions." Imler et al. (Gene Ther. 3(1): 75-84, 1996) disclose that "the exact nature of adenovirus sequences present in 293 cells is not known" (page 76, bottom of col. 1), and "many previous attempts to establish stable cell lines permanently expressing the E1 region failed, apparently owing to the toxicity of E1A gene products" (page 76, col. 2, full para. 1). Imler et al. disclose that while vectors expressing E1A under control of a constitutive promoter could be maintained in A549 cells, they could not be maintained in Vero cells (para. bridging pages 76-77).

Given the recognized cytotoxicity of the E1, E2A and E4 gene products, and given the lack of guidance in the specification regarding how to produce complementing cell lines using any type of promoter other than one which directs low levels of expression except when induced (or derepressed), undue experimentation would have been required by one skilled in the art at the time the application was filed to make or use the claimed invention except wherein the host cell

nucleic acid sequences encoding products complementing the deficiencies in the E2A or E4 region are operably linked to inducible or repressible promoters.

This rejection would be overcome by amending claims 53 and 63 to indicate that the E2A and E4 complementing sequences in the cell are operably linked to an inducible or repressible promoter. For example, see claims 147 and 176 presented in the reply of 5/5/03 in 09/261,922.

Interference

Claims 53-58, 63-68, 73-78, 81-86, and 91-98 are rejected under the principles of *res judicata* and collateral estoppel as being not patentably distinguishable from count 1 in Interference No. 105046 involving Applicant's patent US 5,994,106 and Imler et al. application 09/725,720 (US 2001/0049136), now US Pat. No. 7,005,277, which count was lost to Applicant (see *In re Deckler*, 24 USPQ2d 1448 (Fed. Cir. 1992));

or alternatively, under the principle of estoppel under then 37 CFR 1.658(c) (now 37 CFR 41.127(a)(1)) for failing to move under then 37 CFR 1.633 (now 37 CFR 41.121) to add the instant application or its claimed subject matter to the '046 interference (see MPEP 2363.03).

Instant claims 63-68, 81-86, and 95-98 are directed to methods for propagating an adenoviral vector deficient in one or more of all essential gene function of the E1 region, and at least one essential gene function of E2A and/or at least one essential gene function of E4 on a cell line that complements the deficiencies but wherein there is no overlap between the vector genome and cell genome that mediates homologous recombination to result in a replication competent adenoviral (RCA). Claims 53-58, 73-78, and 91-94 are directed to systems of a vector and cell corresponding to the vector and cell used in claims 63-68, 81-86, and 95-98.

Claims 1-24 of the '106 patent were designated as corresponding to count 1 in the '046 interference. The instant claims do not define an invention that is patentably distinguishable from that of claims 11-24 of the '106 patent. Claims 11-20 are directed to stocks of adenovirus free of replication competent adenovirus produced by propagation in a cell line that complemented deficiencies in one or more of E1, E2A and E4, wherein there is insufficient overlap between the vector genome and cell genome to allow homologous recombination to produce a replication competent adenoviral vector, i.e. the method and the system used to make the stocks are described in the lost stock claims themselves. Claims 21 and 22 are directed to systems where E1 and E2A or E1, E2A and E4, respectively are complemented without sufficient overlap between the vector and cell genome for production of RCA, and claims 23 and 24 are directed to the methods of propagation using the systems without producing RCA. The instant limitation that there is no overlap between the vector genome and cell genome that mediates homologous recombination to result in a RCA is essentially the same as the limitation in the patent claims that there is insufficient overlap between the vector genome and cell genome to allow homologous recombination to produce a RCA.

Most of the instant dependent claims limit the broadest invention to embodiments that are evident from the base claims where various combinations of E1, E2A and E4 are complemented. The claims of the '106 patent were not limited to adenoviral vectors with deficiency in all essential gene function of E1 (or E2A or E4), but such embodiments are suggested by the patent claims that explicitly recite that one or more essential gene functions of each of the E1, E2A, and E4 regions be deficient in the vector and complemented by the cell. Thus, the limitation in the instant claims limiting the invention to embodiments to those where the adenoviral vector is

deficient in all essential E1 gene functions does not define an invention that is patentably distinguishable from that of claims 11-24 of the '106 patent or the count of the '046 interference.

Instant claims 91-98 limit the adenoviral vector to one based on a human adenovirus or human Ad5 specifically. These limitations do not define an invention patentably distinguishable from that of the claims of the '106 patent or the count of the '046 interference because at the time the invention was made the predominant adenovirus used for making adenoviral vectors were human adenovirus, and Ad5 specifically.

Even if the inclusion of the limitations that all essential E1 gene functions be deficient and complemented or that the adenovirus be derived from a human adenovirus or Ad5 would define an invention separately patentable form the count lost in the '046 interference, Applicant is estopped from pursuing this subject matter for having failed to move, under then 37 CFR 1.633, to add the instantly claimed subject matter to the '046 interference. Imler's application 09/725,720, the winning party of the '046 interference, also discloses adenovirus vectors deleted for all of E1, including E1A and E1B and derived from Ad5 (see for example pages 6-8, page 10, lines 14-23 of the '720 specification as filed, or its corresponding published application US 2001/0049136 at ¶¶ 0022-0036, 0045). Instant claims 57, 67, 77, and 85 in reciting that the complementing cell contains at least ORF6 of E4 embraces inclusion of all E4 ORFs, as disclosed in the instant specification and that of the '720 Imler application at page 17 and Example 8 (US 2001/0049136 at ¶¶ 0081-86, and Example 8). The Imler '720 application, Example 8, making a cell line where the E4 complementing DNA is Ad5 nucleotides 32800-35463 or 32800-35826. Imler's Example 4 describes making E1 and E4 deleted Ad5 vectors where the E4 deficiency is nucleotides 32800-35826. There is no overlap between these E4

complementing sequences in the cell lines and the E4 deleted Ad5 vector. Thus, propagating adenoviral vectors with this E4 deficiency in the E4 complementing cells taught would not form RCA.

Claims 59, 60, 69, 70, 79, 80, 87, and 88 are rejected under the principles of *res judicata* and collateral estoppel as being not patentably distinguishable from count 1 in Interference No. 105046 involving Applicant's patent US 5,994,106 and Imler et al. application 09/725,720 (US 2001/0049136), now US Pat. No. 7,005,277, which count was lost to Applicant (see *In re Deckler*, 24 USPQ2d 1448 (Fed. Cir. 1992).

These claims limit the invention to embodiments wherein complementation of an E4-deficiency of an adenoviral vector is carried out in a cell line with E4 ORF6 and no other E4 ORF. This limitation does not define an invention patentably distinguishable from the count of the '046 interference because at the time the invention was made it was known that E4 ORF6 alone was sufficient to complement a deletion of the entire E4 region for replication and propagation of an E4-deleted adenovirus. The instant application is a CON of application 08/258,416, which presented claims directed specifically to the cell lines comprising sequences that complement essential gene functions deleted from the E4 region of an adenoviral vector that are required in the system and methods of the instant claims. Claims 39, 45, 48, 51, and 94 of the '416 application required the cell line to contain E4 ORF6 and no other E4 ORFs, as in the instant claims. The '416 application was involved in Interference Nos. 104,825 and 104,829 including the claims directed to generic E4 complementing cell lines and where the E4 complementing sequence was limited to E4 ORF6. The Board held in both interferences, citing

Cutt et al. (J. Virol. 61(2): 543-552, Feb. 1989), Ketner et al. (Nucleic Acids Res. 17(8): 3037-3048, 1989), Bridge et al. (J. Virol. 63(2): 631-638, Feb. 1989), and Bridge et al. (Virol. 193: 794-801, 1993), that the claims of the '416 application limiting the E4 complementing sequence to E4 ORF6 were not patentably distinguishable over the counts directed to cells with a generic E4 complementing sequence. See pages 9-23 of "Memorandum Opinion and Order", Paper No. 89 of Interference No. 104,825, filed 9/3/03 and pages 18-33 of "Memorandum Opinion and Order", Paper No. 74 of Interference No. 104,829, filed 2/12/03, which are incorporated herein as grounds of rejection.

These rejections based on interference estoppel would be overcome by limiting the claims such that there was no overlap between the adenoviral genome of the vector and adenoviral complementing sequences of the cell line that would mediate recombination, as previously claimed, not simply recombination that would result in RCA. All that is required to prevent homologous recombination between adenoviral sequences of the vector and cell genome leading to formation of an RCA is where there is insufficient overlap to mediate homologous recombination that would restore one deficiency in the vector, since all of the E1, E2A or E4 deficiencies of in the vector are deficiencies of essential functions (for replication). The presence of any one of the deficiencies is sufficient to result in a replication defective vector. Consequently, the limitation of the interference count did not preclude restoring one of two or two of three recited deficiencies, it only precluded restoring all the recited deficiencies.

There is no suggestion in the prior art or in Imler that would motivate one of skill in the art to insure that there would be no overlap between the adenoviral sequences of the vector and

cellular genome that mediates homologous recombination, i.e. no deficiencies in the vector could be restored by homologous recombination.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 53-60, 63-70, 73-88, and 91-98 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 147, 159, 160, 176, 188, 189, 207-225 of copending Application No. 09/261,922. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of '922, in particular claims 209, 211, 213, 215, 217, 219, 222, 224, 226, 228, 230, and 232, are directed to an invention that is embraced by the instant claims wherein the cell line is an A549 cell and the E1 complementing sequence has a particular structure. Although none of the '922 claims explicitly recite that the E4 complementing sequence be only E4 orf6, the supporting

disclosure in the '922 application teaches to use such an E4 complementing, and as indicated above in the rejection of claims 59, 60, 69, 70, 79, 80, 87, and 88 based upon interference estoppel, such a complementing sequence would have been an obvious variant in any case since it was known in the prior art that E4 orf6 was sufficient to complement deletion of the entire E4 region.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. The '922 application has been allowed. Upon issuance, this rejection will no longer be provisional.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe, Ph.D. whose telephone number is (571) 272-0733. The examiner can normally be reached on M-F, 8:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Primary Examiner
Art Unit 1633